IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

IN RE BIOGEN '755 PATENT LITIGATION	Hon. Claire C. Cecchi Civil Action No. 10-2734 (CCC/JBC) (consolidated)

BIOGEN'S MEMORANDUM OF LAW IN OPPOSITION TO BAYER'S MOTION FOR SUMMARY JUDGMENT OF INVALIDITY NO. 3 – LACK OF WRITTEN DESCRIPTION

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INTRODUCTION

The "written description" requirement of 35 U.S.C. § 112 asks whether the patent application "reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharm., Inc.* v. *Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*). It is a question of fact, both as to the underlying questions (*e.g.*, what the patent discloses) and as to the ultimate conclusion of whether the disclosure would convey to a skilled artisan that the inventor possessed the claimed subject matter. *See*, *e.g.*, *WBIP, LLC* v. *Kohler Co.*, 829 F.3d 1317, 1337–38 (Fed. Cir. 2016). Bayer must prove a lack of written description by clear and convincing evidence. To get summary judgment, then, Bayer must show either that U.S. Patent No. 7,588,755 (the "Fiers '755 Patent") lacks written description as a matter of law, or that its evidence is so overwhelmingly powerful that the only conclusion a reasonable jury could reach is that the patent lacks written description. *See Trimed, Inc.* v. *Stryker Corp.*, 608 F.3d 1333, 1340 (Fed. Cir. 2010).

Bayer does not come close to meeting that standard. Bayer stumbles at the first step, by suggesting that the Fiers '755 Patent claims a group (or "genus") of related items, namely interferon-beta ("IFN-β") and mutated versions of IFN-β (or "muteins"). It does not. As the Court found on claim construction, the Fiers '755 Patent claims ***methods of treatment*** using recombinantly produced IFN-β and IFN-

β-like polypeptides. The Patent Office concluded that these method-of-treatment claims are patentably distinct from claims to the polypeptides themselves. Indeed, the patent to the polypeptides was awarded to another group of inventors, while Dr. Walter Fiers got the method-of-treatment patent. All of Bayer's arguments assume that a skilled artisan would be seeking to create an IFN-β-like polypeptide, rather than seeking to determine whether such a polypeptide has biological activity such that it can be used in a method of treatment.

Even accepting Bayer's arguments on their terms, however, Bayer is still wrong to argue that a genus claim necessarily lacks written description where the patent describes only one member of that genus (a "species"). There is no such rule. Quite the contrary: "There is no categorical rule that a species cannot suffice to claim the genus." *Hynix Semiconductor Inc.* v. *Rambus Inc.*, 645 F.3d 1336, 1352 (Fed. Cir. 2011). The cases on which Bayer relies simply reflect that, as a matter of fact, the disclosures in those patents were insufficient. Whether the Fiers '755 Patent describes sufficient species to claim a genus is an entirely different question of fact, and one that is hotly contested.

And on the facts here, the record evidence is far more than enough for Biogen to overcome summary judgment and to require Bayer to prove its written-description defense to a jury. That record evidence comes in multiple forms:

The patent itself: Bayer asserts that the Fiers '755 Patent does not provide

sufficient written description of the variants of IFN-β that can be used to practice the method-of-treatment claims at issue here. Biogen disagrees. The patent discloses IFN-β muteins can have the biological and immunological activity of natural, human IFN-β. *See, e.g.*, Decl. of Steven M. Balcof Ex.[1]1 (Fiers '755 Patent), col. 7:2–7. Moreover, the patent discloses that biologically active interferon shares a common structural core, *see, e.g.*, *id.* col. 4:39–46, and thus biologically active IFN-β muteins must also have that common structural core. The patent goes on to disclose various examples of IFN-β muteins that might have the biological and immunological activity of native human interferon-beta ("HuIFN-β"), including variants that may be found in nature (or, "polymorphs"), *see, e.g.*, *id.*, col. 2:32–39, and variants with one or more amino acid substitutions that can improve stability or solubility, *see, e.g.*, *id.*, col. 48:22–27.

The prosecution history: The Fiers '755 Patent spent over twenty years in the Patent Office, scrutinized by Senior Level Examiner James Martinell, Ph.D. Biogen overcame repeated challenges to the patent application, on any number of aspects of patentability. Notably, however, Examiner Martinell never once suggested what Bayer now argues is indisputable, that there was a written-description problem. On the contrary, Examiner Martinell agreed with Biogen that

[1] Unless otherwise stated, all citations to exhibits ("Ex.") refer to exhibits to the Declaration of Steven M. Balcof in Support of Biogen's Oppositions to Defendants' February 3, 2017 Summary Judgment Motions.

the Fiers '755 Patent specification discloses and enables a range of recombinant polypeptides that display "the antiviral activity of human" IFN-β, as well as their composition and methods of use. *See* Ex. 40 ('843 Appl, 9/18/97 Response) at 5; Ex. 41 ('843 Appl., 12/22/00 Patent Office Communication) at 1.

The experts: Bayer's experts opine that the disclosure of the Fiers '755 Patent is too meager to support a claim to a genus of IFN-β muteins. But Biogen's equally-well-credentialed experts disagree. These include Dr. Michael R. Green, who is a professor of molecular, cell, and cancer biology at the University of Massachusetts (and the first author of one of the preeminent laboratory manuals for molecular biologists), and Dr. K. Christopher Garcia, a professor of molecular and cellular physiology and of structural biology at Stanford University. Having reviewed the specification of the Fiers '755 Patent and the state of the art at the time, they will testify that the Fiers '755 Patent ***does*** adequately teach a skilled artisan that Dr. Fiers possessed methods of treatments with the genus of muteins.

From the patent itself, its prosecution history, and the companion expert testimony, a reasonable jury could reject Bayer's written-description challenge, either by rejecting Bayer's argument outright or by deciding that there is conflicting evidence and that Bayer's evidence is not clear and convincing. Bayer's summary judgment motion should therefore be denied.

STATEMENT OF FACTS

Biogen draws these facts from the Fiers '755 Patent, its prosecution history, the accompanying affidavits of Dr. Green and Dr. Garcia and their exhibits, and from Bayer's exhibits. As addressed in detail below, the key facts—those relating to which recombinantly expressed polypeptides and their therapeutic uses are disclosed in the Fiers '755 Patent—are all disputed.

IFN-β and Its Muteins

IFN-β is a protein found in infinitesimal amounts in human bodily fluids. *See* Decl. of Michael R. Green ("Green Decl.") ¶ 44. For decades it was thought to have significant promise as a method of treatment. *See generally id*. ¶ 48. Much of this trial will be about the history of attempts by leading scientists, including Dr. Fiers, then of Biogen, to identify the DNA sequence for IFN-β, to create IFN-β recombinantly—that is, in a host cell other than a human cell—and to determine whether recombinantly created IFN-β has biological activity like that of HuIFN-β.

Like any protein, IFN-β is made up of building blocks called "amino acids." Green Decl. ¶ 32. The complete ("mature") form of HuIFN-β comprises 166 amino acids. Those amino acids, in turn, are created from a DNA sequence that, like all DNA sequences, includes a specific array of four possible "bases," abbreviated A, C, T, and G. The DNA sequence is read in three-base units called "codons." *Id.* ¶ 32. For example, the sequence "AGC" codes for (or, "encodes")

the amino acid serine. With three positions in a codon and four possible bases at each position, there are 64 possible combinations. There are, however, only 20 amino acids created from DNA. This results in a phenomenon called "degeneracy," in which more than one three-base codon can encode the same amino acid. To use the same example, serine is encoded not only by the sequence AGC, but also by the sequences TCA, TCG, and others. *Id.*

Dr. Fiers elucidated a DNA sequence that creates HuIFN-β. Dr. Tadatsugu Taniguchi elucidated a slightly different DNA sequence that creates HuIFN-β. The Fiers '755 Patent teaches that those different DNA sequences create the same amino-acid sequences; the DNA sequences are degenerate. *See* Ex. 1 (Fiers '755 Patent), col 5:58–61.

Bayer uses the term "mutein" to refer to variants of IFN-β created by DNA that differs from the IFN-β DNA that Dr. Fiers found. Those muteins can have amino-acid sequences that vary from that of HuIFN-β—*e.g.*, one amino acid can be changed for another, or an amino acid can be added or removed.

As the Court recognized in its claim construction opinion (D.I. 403 at 1), HuIFN-β is a special kind of protein called a "glycoprotein," meaning that it has sugars ("glycans") bound to its amino acids via a process called "glycosylation." And the glycans themselves—a branched shape of connected sugars—can vary from protein to protein and from species to species. Green Decl ¶ 53; Garcia Decl.

¶¶ 51-54. Thus, glycoproteins made in humans will tend to have certain glycosylation patterns, while other host cells will attach a different mix of glycans in a different glycosylation pattern. *Id*.

Glycans play various roles in glycoproteins. They may be necessary, for example, for the protein's biological activity. Green Decl. ¶ 76; Garcia Decl. ¶ 31, 37. A protein is biologically active only if it bonds appropriately with its receptor. Biological activity can be affected by a protein's three-dimensional folded shape, and whether and how it is glycosylated. Green Decl. ¶ 37; Garcia Decl. ¶¶ 23, 31, 37.

Before Dr. Fiers's invention, it was not known whether the glycan in HuIFN-β was a prerequisite for that protein's biological activity. Green Decl. ¶¶ 55, 69-78, 85; Garcia Decl. ¶¶ 23, 31-41. It was therefore also not known whether recombinantly expressed IFN-β made in a non-human host cell, which might glycoslate IFN-β differently or not at all, would be biologically active. *Id*. Dr. Fiers recombinantly expressed IFN-β in *E. coli*, a bacterial strain that does not glycosylate proteins at all. Green Decl. ¶ 53, 96; Garcia Decl. ¶¶ 43, 56, 70. He determined that the resulting IFN-β was, in fact, biologically active, and thus that the glycan in HuIFN-β was not necessary for biological activity. Ex. 1, col. 40:34–46:38; Green Decl. ¶ 53, 96; Garcia Decl. ¶¶ 43, 56, 70. That finding forms a basis for Dr. Fiers's claimed invention of the therapeutic use of recombinantly expressed

IFN-β-like proteins, with no glycans or different glycans, that have the biological activity of HuIFN-β.

Claim 1 of the Fiers '755 Patent

Reflecting Dr. Fiers's invention, the Fiers '755 Patent is directed to the therapeutic use of recombinantly expressed IFN-β and IFN-β muteins that are biologically active like natively sourced HuIFN-β. Claim 1, which Biogen asserts against Bayer, includes three requirements for the administered IFN-β polypeptide, which Biogen has bolded in the text below for the Court's convenience:

> 1. A ***method for immunomodulation or treating*** a viral conditions, a viral disease, cancers or tumors ***comprising*** the step of ***administering*** to a patient in need of such treatment a therapeutically effective amount of a composition comprising:
>
> ***a recombinant polypeptide produced by a non-human host*** transformed by a recombinant DNA molecule comprising a DNA sequence selected from the group consisting of:
>
> (a) ***DNA sequences which are capable of hybridizing*** to any of the DNA inserts of G-pBR322(Pst)/HFIF1, G-pBR322(Pst)/HFIF3 (DSM 1791), G-pBR322(Pst)/HFIF6 (DSM 1792), and G-pBR322(Pst)/HFIF7 (DSM 1793) under hybridizing conditions of 0.75 M NaCl at 68° C. and washing conditions of 0.3 M NaCl at 68° C., and which code for a ***polypeptide displaying antiviral activity***, ...

Ex. 1 (Fiers '755 Patent), col. 49:59–50:12 (emphasis added). Thus:

First, the recombinant polypeptide must be recombinantly "produced by a

non-human host." [2]

Second, the recombinant polypeptide must be made using a recombinant DNA molecule that contains DNA sequences that are, under specific conditions, "capable of hybridizing to any of the DNA inserts" in Claim 1. Those inserts include almost all of the DNA sequence that encodes HuIFN-β.

Biogen will show at trial, and Bayer will attempt to disprove, that the conditions required by Claim 1—the hybridization and washing conditions—are sufficiently stringent that only DNA sequences that are almost identical, or "homologous," can hybridize to each other. *See, e.g.*, Ex. 1 (Fiers '755 Patent), col. 23:19–24:39; 26:63–27:4; Green Decl., ¶ 126; *see also* Ex. 21 ('930 Appl., 12/23/08 Amendment). Thus, Biogen will show at trial that Claim 1 requires that the recombinant polypeptide be made using a DNA molecule that is nearly identical to a DNA that encodes HuIFN-β, and thus that the recombinant polypeptide will necessarily have an amino acid sequence that is identical or nearly identical to that of HuIFN-β.

Third, the recombinant polypeptide must display "antiviral activity," which is the hallmark of HuIFN-β activity. *See* Ex. 1 (Fiers '755 Patent), col. 3:4–16;

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[2] This requirement is not at issue on this motion, although it is relevant to Bayer's Second Motion for Summary Judgment (which asserts that the Fiers '755 Patent is anticipated by prior-art treatment using natively sourced HuIFN-β), to Bayer's Fourth Motion for Summary Judgment (which asserts that the Fiers '755 Patent is anticipated by a patent to Dr. David Goeddel), and to Serono's Motion for Summary Judgment of Invalidity Under 35 U.S.C. § 112.

Green Decl. ¶¶ 123, 125. For a recombinant polypeptide to have HuIFN-β-like antiviral activity, it must be folded into a three-dimensional structure similar to that of HuIFN-β. Green Decl. ¶¶ 34-37, 73. The patent itself teaches this. *See, e.g.*, Ex. 1 (Fiers '755 Patent), col. 1:19–24.

Bayer's IFN-β Mutein

Bayer's Betaseron® product is a recombinant polypeptide, the use of which is within the scope of Claim 1 of the Fiers '755 Patent. *See* Br. at 6, 20; [3] Ex. 95 (Bayer's Response to Request for Admission), No. 3. Betaseron—also known as IFN-β-1b—is an IFN-β mutein that differs from HuIFN-β by only two amino acids. Betaseron lacks the last amino acid on one end of the HuIFN-β polypeptide, and has a serine as its 17th amino acid instead of the naturally-occurring cysteine. *See* Green Decl. ¶ 126; Ex. 65 (Ravetch Rep.) ¶ 673.

Despite these minor variations, Betaseron has the delineated characteristics of the recombinant polypeptide utilized in Claim 1. It is made in *E. coli*, a non-human host. Ex. 59 (Betaseron® Label), at 9. It has antiviral activity akin to HuIFN-β. *See* Br. at 20; Ex. 6 at 9; *see also* Green Decl. ¶ 126. And it is encoded by DNA that is capable of hybridizing to the IFN-β DNA inserts identified in Claim 1. *See* Br. at 6; Green Decl. ¶ 126.

[3] Unless stated otherwise, all references to "Br." are to Bayer's opening brief [D.I. 510-7].

The Fiers '755 Patent Disclosure of IFN-β Muteins

Despite the close similarity between its own Betaseron product and IFN-β, Bayer complains that Claim 1 encompasses treatment with a broad range of potential IFN-β muteins, and that the specification of the Fiers '755 Patent does not teach an ordinarily skilled artisan that Dr. Fiers possessed the full scope of the muteins that could be used to practice that claim. Biogen therefore focuses its description of the patent specification on portions relevant to that argument.

Description of IFN-β Muteins and Their Use

At trial, the jury will hear testimony about IFN-β muteins from two of Biogen's experts, Dr. Green and Dr. Garcia.

Dr. Green is the Chair and Professor of Molecular, Cell, & Cancer Biology, a Professor of Molecular Medicine and Biochemistry & Molecular Pharmacology, and the Director of the University of Massachusetts Medical School Cancer Center. Green Decl. ¶ 7. In addition, he was selected to be a Howard Hughes Medical Institute investigator, a group of around 300 scientists currently including 25 Nobel laureates and 182 members of the National Academy of Sciences. Green Decl. ¶ 13. In 1980, Dr. Green was actively researching gene expression as a graduate student. Green Decl. ¶ 9.

Dr. Garcia is a Professor of Molecular and Cellular Physiology and of Structural Biology at Stanford University. Decl. of K. Christopher Garcia ("Garcia

Decl.") ¶ 5. Dr. Garcia is also a member of Stanford's Cancer Institute and of Bio-X, Stanford's interdisciplinary biosciences institute focused on research connected to biology and medicine. He, too, is a Howard Hughes Medical Institute investigator. Dr. Garcia is considered a leading expert in recombinant glycoprotein expression, interferon receptor structure, and engineering proteins such as IFN-β. *Id*.

As Dr. Green and Dr. Garcia will explain to the jury, the Fiers '755 Patent explicitly discloses the use of recombinant IFN-β muteins with biological activity akin to HuIFN-β: "It is this expression in a host of polypeptide(s) displaying an immunological or biological activity of HuIFN-β and the methods, polypeptides, genes and recombinant DNA molecules thereof, which characterize this invention." Ex. 1 (Fiers '755 Patent), col. 6:2–5; *see also id.* col. 6:54–7:7, 15:11–14. For example, the Fiers '755 Patent discloses various recombinant DNA molecules that could be used to express IFN-β and/or IFN-β muteins, *id*. col. 29:64–34:67, and that those recombinant DNA molecules could express IFN-β or IFN-β-like polypeptides that have HuIFN-β-like biological activity, *id*. col. 35:1–42:19.[4]

[4] The Fiers '755 Patent contains additional disclosure of the use of biologically active IFN-β and IFN-β muteins. *See, e.g.*, *id*. at 6:8–36, 15:4–10. Although these statements were not in the British June 6, 1980 priority application, they provide further evidence that Dr. Fiers contemplated the use of IFN-β muteins that are structurally similar to HuIFN-β.

The parties dispute whether or not these recombinantly expressed polypeptides were mature IFN-β. Biogen contends that those polypeptides could be mature IFN-β or could be a longer or shorter IFN-β muteins ("IFN-β fusions") with IFN-β-like activity. *See* Green Decl. ¶ 126; Ex. 75 (Green Dep., 1/12/17) 483:11–24, 551: 2–18; Ex. 73 (Garcia Dep.) 87:23–88:14. Confusingly, Bayer seems to contend both that those polypeptides ***must be*** IFN-β itself and that they are IFN-β ***muteins***. *Compare* Br. at 18 *with id*. at 18–19, 19 n.3. For purposes of this motion, it does not matter which interpretation is correct. Both sides agree that Dr. Fiers at least contemplated the use of recombinant IFN-β and IFN-β muteins that have IFN-β-like activity. Thus, as Dr. Green and Dr. Garcia will testify at trial, the Fiers '755 Patent described numerous working examples of recombinant polypeptides. Green Decl. ¶ 100-102; Garcia Decl. ¶¶ 55-68.

Moreover, Dr. Green and Dr. Garcia will testify that the Fiers '755 Patent teaches that once it was properly demonstrated that recombinantly expressed IFN-β has biological and immunological activity like HuIFN-β, one could also use related DNA sequences to express related IFN-β muteins with IFN-β-like activity. For example, the Fiers '755 Patent states: "it is only after such HuIFN activity is shown that the DNA sequence, recombinant DNA molecule or sequences related to them may be usefully employed to select other sequences corresponding to HuIFN in accordance with this invention or to produce recombinant DNA molecules that

may express products having an immunological or biological activity of HuIFN-β." Ex. 1 (Fiers '755 Patent), col. 6:23–29.

Dr. Green and Dr. Garcia will also explain that the Fiers '755 Patent discloses at least two categories of IFN-β muteins that would have IFN-β-like activity: IFN-β variants that are naturally found in humans (polymorphs) and IFN-β muteins that have one or more amino acid differences from native IFN-β that may have slightly altered properties such as increased stability or solubility. *See, e.g.*, Ex. 1 col. 2:32–39, 24:25–39, 25:54–26:3, 48:7–27; *see also id*. col. 6:8–36; Green Decl. ¶¶ 112, 124-125; Garcia Decl. ¶¶ 57-68.

Biogen's experts will explain that for both of these categories, the Fiers '755 Patent makes clear that the IFN-β muteins must be closely related to HuIFN-β. For example, regarding polymorphs, the Fiers '755 Patent disclosed that natural variations in IFN-β in the human population could be biologically active. *Id*. col 2:32–39, 25:59–26:3. Protein polymorphism is not limited to IFN-β. Indeed, the structurally related protein, interferon-alpha ("IFN-α"), is polymorphic and several of its variants are (and were known to be) biologically active. Green Decl. ¶ 112. Moreover, the Fiers '755 Patent taught that the DNA sequence that Dr. Taniguchi elucidated for IFN-β was different from the DNA sequence that Dr. Fiers elucidated for IFN-β. *See* Ex. 1 (Fiers '755 Patent), col. 5:58–61, 25:62–26:3 (noting that the amino acid sequence is the same, *i.e.*, that the Taniguchi DNA

sequence and the Fiers DNA sequence are degenerate). According to Dr. Green and Dr. Garcia, a person of ordinary skill in the art would understand that Dr. Fiers possessed how to use the disclosed IFN-β DNA inserts to find IFN-β polymorphs, recombinantly express those polymorphs, and use the recombinantly produced polymorphs with the requisite antiviral activity. *See, e.g.*, *id.* col. 6:23–29, 7:2–7, 26:63–67; *see also* Green Decl. ¶¶ 112, 124-125; Garcia Decl. ¶¶ 58-59.

Regarding the minor variants, Dr. Green and Dr. Garcia will testify at trial that the Fiers '755 Patent disclosed IFN-β muteins with one or more amino acid replacements and muteins that are longer or shorter than IFN-β that can have the biological activity of HuIFN-β. Ex. 1 (Fiers '755 Patent), col. 48:22–27; *see also id*. col. 6:8–36, 15:1–10. For example, the Fiers '755 Patent taught that such minor variants could possibly "increase the stability, increase the solubility, increase the antiviral activity, increase [the] 2,5-A synthetase activity or increase the host specificity range." *Id*. col. 48:22–27. Indeed, the Fiers '755 Patent states that once it was determined that a polypeptide is biologically active, it was common at the time to make muteins: IFN-β muteins could be made "by well-known means." *Id*. col. 48:36–41.

Thus, the Fiers '755 Patent discloses a genus of closely related IFN-β muteins with HuIFN-β-like activity that could be used in methods of treatment.

Description of the Structure and Biological Activity of IFN-β Muteins

Biogen's experts will also testify at trial that the Fiers '755 Patent taught a skilled artisan that the IFN-β muteins of Dr. Fiers's invention are related to IFN-β both by their structure (what they are) and by their biological activity (what they do). For example, the Fiers '755 Patent discloses that the IFN-β muteins have "amino acid sequence[s] and composition[s] [that] are substantially consistent with human fibroblast interferon and which have an immunological or biological activity of human fibroblast interferon." Ex. 1 (Fiers '755 Patent), col. 1:19–24.

Dr. Green and Dr. Garcia will also testify that at the time of Dr. Fiers's invention, certain salient features of the structure of HuIFN-β were known in the prior art. For example, it was known that IFN-β has a disulfide bond that is necessary in order for the polypeptide to display antiviral activity. Green Decl. ¶ 69, 79; Garcia Decl. ¶ 62, 64. A disulfide bond forms between two cysteine amino acids. Because IFN-β has one disulfide bond, at least two of its three cysteines are necessary for IFN-β to be biologically active.

In addition, the Fiers '755 Patent disclosed that IFN-β and IFN-α "may share a common active core" such that both IFN species could interact with common receptors in similar ways. *See* Ex. 1 (Fiers '755 Patent), col. 4:39–46. Thus, Dr. Green and Dr. Garcia will testify that the Fiers '755 Patent taught that IFN-β and IFN-α folded into structurally similar three-dimensional structures, which was

necessary for their common biological activity, including antiviral activity. *See* Ex. 67 (Bell Dep. Tr.) 78:12–79:7.

Dr. Garcia will present evidence that at the time of Dr. Fiers's invention in June of 1980, an ordinarily skilled artisan understood much about the common structural core of IFN-β and IFN-α based on the elucidation of the DNA sequence that encodes HuIFN-β and IFN-α, as well as their corresponding amino acid sequences. For example, by comparing the DNA and amino acid sequence of IFN-β and IFN-α, scientists had determined "that there is a strong selective pressure favouring the conservation of several amino acids" in IFN-β and IFN-α. Ex. 96 (Tadatsugu Taniguchi & Weissmann *et al., Human Leukocyte and Fibroblast Interferons are Structurally Related*, 285 Nature 547, (1980)) at 547.[5] "It is quite likely that at least some of the conserved amino acids are essential for a function common to Le-IL [IFN-α] and F-IF [IFN-β], perhaps the induction of the virus-resistant state of the target cell. These findings may provide guidelines for the tailoring of modified, possibly shorter polypeptides possessing certain activities of interferon." *Id*. Thus, a skilled artisan would have known that certain amino acids were common to IFN-β and IFN-α and therefore likely necessary for biological activity, *see* Ex. 67 (Bell Dep.) 102:07–103:8, while other amino acids were likely not necessary and thus could be varied using known conservative substitutions.

[5] The parties agree that pre-prints of Dr. Charles Weissmann's article were in circulation at least by May of 1980.

See Garcia Decl. ¶¶ 62, 64-65. Similarly, using the known computational models at the time, a skilled artisan would be able to make and test predictions about the structure and function of IFN-β (and IFN-α). *See, e.g.*, Ex. 67 (Bell Dep.) 114:2–23; Garcia Decl. ¶ 63-65. Based on this information, a person of skill in the art would be reasonably able to predict which IFN-β muteins would be likely to preserve IFN-β-like activity. *See* Garcia Decl. ¶ 63-.

Moreover, the Fiers '755 Patent ***itself*** disclosed a robust panel of assays to determine whether reasonably predictable IFN-β-like muteins in fact have antiviral activity. *See* Ex. 1 (Fiers '755 Patent), col. 36:1–45:52. Each of Biogen, Serono, and Bayer use one of those assays as a condition to releasing batches of their IFN-β products for therapeutic use, *see, e.g.*, Ex. 57 (Avonex® Label); Ex. 58 (Rebif® Label); Ex. 59 (Betaseron Label); Ex. 60 (Extavia® Label), thus demonstrating that even today, nearly forty years later, the teaching of the Fiers '755 Patent provides a quick and accurate way to identify biologically active IFN-β.

The Prosecution History of the Fiers '755 Patent

Just as the specification of the Fiers '755 Patent refutes Bayer's written-description argument—or at least, as relevant here, creates a genuine issue of fact about the sufficiency of the written description—so, too, does the prosecution history of the Fiers '755 Patent and its patent family.

The jury will hear that the application that led to the Fiers '755 Patent,

U.S.S.N. 08/449,930, was filed in 1995, and was examined by Senior Level Examiner James Martinell, Ph.D. Examiner Martinell was intimately familiar with the disclosure of the Fiers '755 Patent; he examined that patent, and related patent applications, for nearly 30 years. One of the first things that Examiner Martinell did in assessing Dr. Fiers's patent applications was to issue a "restriction requirement," in which he asserted that claims to the DNA sequence for IFN-β, claims to the recombinant proteins themselves, and claims to methods of treatment are patentably distinct, and in which he required Dr. Fiers to seek those claims separately. *See,* Ex. 26 ('609 Appl., 4/15/82 Office Action). The jury will hear that over the ensuing decades, the patent for the DNA sequence was awarded to Dr. Taniguchi's group, the patent for the recombinant proteins themselves was also awarded to Dr. Taniguchi's group, and the patent for methods of treatment—the patent in suit here—was awarded to Dr. Fiers. *See* Ex. 84 (Newland Dep.) 90:2–91:14; Ex. 70 (Deluca Dep., 8/15/12) 92:1–23.

The jury will also hear significant testimony about the many concerns Examiner Martinell raised, the rejections he issued, and how Biogen successfully overcame those rejections by demonstrating the correctness of Biogen's positions. *See, e.g.*, Ex. 76 (Haley Dep.) 225:20–227:13, 296:10–297:17, 299:14–20; Decl. of John Doll ("Doll Decl.") ¶¶ 23-37. Importantly, however, the jury will not hear a single word about Examiner Martinell rejecting the Fiers '755 Patent for failure to

adequately describe either the use of IFN-β muteins or the IFN-β muteins themselves—the argument Bayer makes here. That is because there was no such rejection. In the 20-plus-year prosecution history, including after the Patent Office published its "Written Description Training Materials" in March 2008 laying out requirements for a written-description rejection, Examiner Martinell did not suggest that the patent lacked written description of the muteins that could be used for treatment. *See generally* Doll Decl. ¶¶ 23-37.

The jury will hear, moreover, that Examiner Martinell did raise a related concern in examining a related patent application, and was persuaded that the Fiers '755 Patent enabled a range of recombinant IFN-β polypeptides that display the antiviral activity of HuIFN-β. Specifically, in 1997—over a decade before the Fiers '755 Patent issued in 2009—Examiner Martinell was examining a sister application in the Fiers family, U.S.S.N. 08/253,843. Importantly, that '843 application contained the same specification as did the application that resulted in the Fiers '755 Patent. At the time, the '843 application included proposed claims that were directed to recombinant polypeptides displaying antiviral activity, and to related compositions and methods of use. Examiner Martinell rejected those claims, asserting that "the disclosure is enabling only for claims limited to human IFN-β." *See* Ex. 102 ('843 Appl., 3/18/97 Office Action) at 2. After receiving Biogen's arguments about the scope of what was enabled, Examiner Martinell

concluded that the specification of the '843 application (and the Fiers '755 Patent) ***did*** disclose and enable a genus of recombinant polypeptides that display "the antiviral activity of human IFN-β," as well as their composition and methods of use. *See* Ex. 40 ('843 Appl., 9/18/97 Response), at 3–4, 5; Ex. 41 ('843 Appl., 12/22/00 Office Action) (noting that the claims are allowable, but the application was suspended for potential interference). The jury will thus learn that Examiner Martinell—presumed by law to be a person of ordinary skill in the art, *Markman* v. *Westview Instruments, Inc.*, 52 F.3d 967, 986 (Fed. Cir. 1995), *aff'd*, 517 U.S. 370 (1996)—determined that the Fiers '755 Patent adequately describes the use of recombinant IFN-β and IFN-β muteins.

The Expert Testimony

Biogen's experts, Dr. Green and Dr. Garcia, agree that the Fiers '755 Patent adequately describes the use of recombinant IFN-β and IFN-β muteins as set forth in Claim 1 of the Fiers '755 Patent. *See* Green Decl. ¶¶ 122-27; Garcia Decl. ¶¶ 58-68.

Both Dr. Green and Dr. Garcia have reviewed the evidence and reviewed Bayer's experts' arguments. Both Dr. Green and Dr. Garcia disagree with the conclusions Bayer draws from the evidence. *See, e.g.*, Green Decl. ¶¶ 25; Garcia Decl. ¶¶ 13. For example, Dr. Green opined that he disagreed with Bayer's experts, Dr. Harvey Lodish and Dr. Leslie D. Bell, regarding the scope of Claim 1

of the patent: "one of skill in the art would understand the scope of the claims to be narrow—the claims cover the use of polypeptides that are closely related to IFN-β, *e.g.*, polymorphs or variants with one or more point mutations, the biological activity of which can be readily ascertained using the assays disclosed in the Fiers GB Application and the Fiers Patent." Green Decl. ¶ 125. Further, Dr. Green opines that routine methods could be used to ascertain or predict which minor variants would be biologically active. *Id*. ¶ 183. Dr. Green goes on to opine that "although I agree that it is not guaranteed that any of the IFN-β variants will be biologically active and thus useful for immunomodulation and as a therapeutic, it would be routine for one to use the assays disclosed in the Fiers GB Application and the Fiers Patent to readily ascertain which polypeptide variants are biologically active." *Id*. ¶ 106.

Similarly, Dr. Garcia opines that "Claim 1 of the Fiers Patent is directed to the use of IFN-β and minor variants in IFN-β." Garcia Decl. ¶ 55 "[A] person of skill in the art would understand that such variants included possible IFN-β polymorphs, conservative mutations, and the standard mutational analysis one undergoes in drug development, not the billions and billions that" Bayer alleges. Garcia Decl. ¶¶ 57-58. Moreover, Dr. Garcia opines that there were many ways that a skilled artisan could predict whether an IFN-β mutein would retain biological activity even without knowing the exact three-dimensional structure of

IFN-β. Garcia Decl. ¶ 63.

ARGUMENT

The "written description" requirement of 35 U.S.C. § 112 asks whether the patent application "reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad*, 598 F.3d at 1351. It assesses whether a skilled artisan can recognize that what the patent claims corresponds to what it describes. *See Alcon Research Ltd.* v. *Barr Labs., Inc.*, 745 F3d 1180, 1191 (Fed. Cir. 2014) (citing *Ariad*, 583 F.3d at 1352).

Whether a patent satisfies the written-description requirement is an issue of fact that must be assessed on a case-by-case basis, *see*, *e.g.*, *Allergan, Inc.* v. *Sandoz Inc.*, 796 F.3d 1293, 1308 (Fed. Cir. 2012); *Lampi Corp.* v. *Am. Power Prods., Inc.*, 228 F.3d 1365, 1378 (Fed. Cir. 2000). There can be subsidiary factual questions, such as the meaning of a particular passage in a patent specification or the teaching of a particular piece of prior art. And the ultimate question—does the patent reasonably convey the inventor's possession of the invention—is itself a question of fact as well. *See WBIP*, 829 F.3d at 1337–38. Judgment calls are reserved for the jury. In *Hynix*, 645 F.3d, for example, the jury rejected the defendant's written-description challenge and the Federal Circuit affirmed the district court's denial of the defendant's subsequent motion for judgment as a matter of law even though the Federal Circuit agreed, "it would certainly be

reasonable to conclude that [patentee]'s claims do not meet the written description requirement." *Id*. at 1352–53.

Moreover, because patents are presumed valid, *see* 35 U.S.C. § 282, Bayer must prove invalidity by clear and convincing evidence, *see Microsoft Corp*. v. *i4i Ltd. P'ship*, 564 U.S. 91, 109–10 (2011); *Summit 6, LLC* v. *Samsung Elecs. Co.,* 802 F.3d 1283, 1294 (Fed. Cir. 2015). On a summary judgment motion, then, Bayer must either prove entitlement to judgment as a matter of law, or "submit such clear and convincing evidence of facts underlying invalidity that no reasonable jury could find otherwise" than in Bayer's favor. *Trimed, Inc.* v. *Stryker Corp.*, 608 F.3d 1333, 1340 (Fed. Cir. 2010) (quoting *SRAM Corp.* v. *AD-II Eng'g, Inc.*, 465 F.3d 1351, 1357 (Fed. Cir. 2006)). The evidence must be viewed in the light most favorable to, "with doubts resolved in favor of," Biogen. *Ethicon Endo-Surgery, Inc.* v. *U.S. Surgical Corp.*, 149 F.3d 1309, 1315 (Fed. Cir. 1998) (citations omitted).

As Biogen shows below, Bayer's motion fails this exacting standard.

I. Bayer's Motion Is Misdirected at the Polypeptides Themselves

One of the themes throughout this motion and the defendants' other summary-judgment motions is a conflation of two patentably distinct inventions: (i) recombinant IFN-β polypeptides themselves and (ii) methods of treatment using those polypeptides. A claim to the polypeptide itself would encompass making,

using, selling, offering for sale or importation of that polypeptide, for any purpose. There ***is*** a polypeptide/protein patent, but it is not Biogen's. It was issued to a Japanese group, now licensed to Serono, and (a fact the defendants omit) Serono is charging Biogen royalties on that patent, which Biogen is paying. The patent in this case, however, is to a method of treatment.

To be sure, there are cases that suggest that a method of treatment claim that merely repackages a claim to the compounds themselves is "little more than a semantic distinction without a difference." *Univ. of Rochester* v. *G.D. Searle & Co.*, 249 F. Supp. 2d 216, 228 (W.D.N.Y. 2003). But this is not such a case, as the Patent Office itself found. Recombinant IFN-β is patentably distinct from methods of use, with the latter depending on proof that recombinant IFN-β had the biological activity of HuIFN-β. Dr. Fiers proved that it did.

His '755 Patent discloses not only a working example of biologically active recombinant IFN-β, but also methods by which he created it, various mutations to IFN-β would likely still result in biological activity, and—crucially—a test by which a skilled artisan in possession of recombinant IFN-β or an IFN-β mutein could determine whether her polypeptide has that biological activity and could thus be used as a method of treatment. That is undisputed. And it is sufficient to inform a skilled artisan that Dr. Fiers "had possession of the claimed subject matter as of the filing date." *Ariad*, 598 F.3d at 1351.

What Bayer seems to be suggesting is that a skilled artisan would need to be able to determine from the patent specification every single IFN-β mutein that would have biological activity. Bayer never explains why that should be the appropriate test for a method-of-treatment claim. On the contrary, the proper test is whether a skilled artisan, reading the patent specification, would recognize that Dr. Fiers knew that some IFN-β muteins would be close enough in structure to HuIFN-β to retain biological activity, and informed the artisan how to test whether her specific mutein has such activity.

Indeed, several district courts have found that the proper inquiry for method of treatment claims is whether the disclosure showed possession of the invention of ***administering*** the drugs, not possession of the genus of drugs. *Erfindergemeinschaft UroPep GbR* v. *Eli Lilly & Co.*, No. 2:15-CV-1202-WCB, 2016 WL 6138124, at *15 (E.D. Tex. Oct. 21, 2016); *see also Regents of Univ. of California* v. *Dako N. Am., Inc.*, No. C 05-03955 MHP, 2009 WL 1083446 (N.D. Cal. Apr. 22, 2009) (determining that the relevant genus for method of use claims is the method itself and not the genus of probes utilized in the method).

But even accepting Bayer's premise, that the Fiers method-of-treatment patent would need to meet the same written-description requirement as the patentably distinct claim to the polypeptides themselves, Bayer's motion fails because there is more than enough evidence from which a jury could find written

description. Biogen turns next to that argument.

II. A Patent Need Not Disclose Multiple Species to Support a Genus Claim

Bayer's brief conveys the impression that disclosure of one species within a genus is, as a matter of law, insufficient to provide written description of a claim to the genus. Bayer thus argues that disclosure of biologically active recombinant IFN-β itself is insufficient to support a claim to methods of treatment using IFN-β muteins. Instead, Bayer argues, a genus may be supported only by disclosing experiments involving a wide swath of IFN-β muteins, or by disclosing an "established" relationship between the structure and the function of IFN-β muteins that will predict with 100% certainty whether a given IFN-β mutein will have antiviral activity. (Br. at 18–25.)

Bayer has the law wrong. It is absolutely permissible for the "description of the invention in the specification" to be "narrower than that in the claim." *In re Smythe*, 480 F.2d 1376, 1382 (C.C.P.A. 1973). Indeed, there is no requirement that any examples be disclosed: "(1) examples are not necessary to support the adequacy of a written description; (2) the written description standard may be met . . . even where actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." *Falkner* v. *Inglis*, 448 F.3d 1357, 1366 (Fed. Cir. 2006). Nor is it improper to claim a range

of DNA sequences and corresponding recombinant polypeptides. *See*, *e.g.*, *Monsanto Co*. v. *Scruggs*, 459 F.3d 1328, 1337 (Fed. Cir. 2006).

What is required is that the patent specification provide sufficient "blaze marks" to guide an ordinarily skilled artisan through the forest of possibilities to the claimed genus. *In re Ruschig*, 379 F.2d 990, 995 (C.C.P.A. 1967). Those blaze marks can include "complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, ***or some combination of such characteristics***." *Enzo Biochem, Inc*. v. *Gen-Probe Inc*., 323 F.3d 956, 964 (Fed. Cir. 2002) (emphasis added). They can include disclosure of the DNA and amino acid sequence of a representative species within a genus of closely related species, and test data demonstrating that species within the genus have the features claimed in the patent. *See Invitrogen Corp.* v. *Clonetech Labs., Inc.*, 429 F.3d 1052, 1073 (Fed. Cir. 2005). In *In re Herschler*, for example, disclosure of a single corticosteroid was sufficient to describe a genus of physiologically active steroids that could be used in practicing the claimed invention. 591 F.2d 693, 701 (C.C.P.A. 1979). Likewise, the "disclosure of a DNA sequence might support a claim to the complementary molecules that can hybridize to it." *Univ. of Rochester* v. *G.D. Searle & Co*., 358 F.3d 916, 925 (Fed. Cir. 2004).

Against this clear authority, Bayer cites *Boston Scientific Corp*. v. *Johnson*

& Johnson, 647 F.3d 1353 (Fed. Cir. 2011), *Wyeth* v. *Abbott Labs.*, 720 F.3d 1380 (Fed. Cir. 2013), and *Carnegie Mellon University* v. *Hoffmann-La Roche Inc.*, 541 F.3d 1115 (Fed. Cir. 2008), as "examples of the Federal Circuit's strict enforcement of the written description requirement as applied to biopharmaceutical genera." (Br. at 14.) None of these cases is on point here.

The patents in *Boston Scientific* (and *Wyeth*) did not provide "any 'definitions, examples, or experimental models . . . for determining whether a compound is a structurally similar analog as contemplated by the patentees.'" *Boston Scientific,* 647 F.3d at 1360 (citation omitted). The Federal Circuit agreed that there was "no guidance at all in the specification as to how to properly identify or choose the claimed analogs." *Id*. at 1365. That is not, then, a categorical rule of law, but simply a conclusion that, on the facts of that case, the defendant had satisfied its factual burden. The Fiers '755 Patent, however, discloses all three things that were absent from the patents in *Boston Scientific* and *Wyeth*:

- The Fiers '755 Patent provides specific contours for the recombinant polypeptide: it must be encoded by DNA molecules that are similar, *i.e.*, capable of hybridizing, to DNA encoding IFN-β and it must have antiviral activity.

- The Fiers '755 Patent provides several examples of recombinant polypeptides of his invention, including the recombinant polypeptide expressed by the specific recombinant DNA molecules constructed by Dr. Fiers, possible IFN-β polymorphs such as Dr. Taniguchi's polymorph, and IFN-β with one or more point mutations (like Bayer's Betaseron).

- The Fiers '755 Patent provides extensive disclosure of how to reliably test for antiviral activity.

In contrast, in *Carnegie Mellon* the patent claimed recombinant plasmids that contain a DNA sequence encoding a bacterial enzyme, DNA Polymerase, but there was undisputed evidence that the genus was so broad as to claim "not a single enzyme, but a family of enzymes encoded by a family of genes that varied from one bacterial species to another." 541 F.3d at 1125. Worse, while the specification explicitly taught that the recombinant plasmids had to be carefully constructed in order to ensure that certain regions of the DNA were "severely damaged or eliminated," the specification did not teach how to damage or eliminate those regions in the various families of enzymes. *Id*. at 1126. The court found a lack of written description not as a matter of law, but as a matter of the facts of that case. The Fiers '755 Patent discloses what the *Carnegie Mellon* patent did not. The Fiers '755 Patent does not claim a family of proteins encoded by a family of genes that vary from claimed species to claimed species. The Fiers '755 Patent claims a method of treatment with a single protein (IFN-β) encoded by a single gene and from a single source (humans) and with closely related recombinant polypeptides. Moreover, the Fiers '755 Patent teaches that the claimed recombinant polypeptides must be encoded by DNA that is nearly identical, if not identical, to the DNA that encodes human IFN-β, and must have antiviral activity like that of human IFN-β.

Rather than *Boston Scientific*, *Wyeth*, or *Carnegie Mellon*, the facts here are much closer to those of *Invitrogen*. In that case, the claims at issue were directed to modified enzymes called reverse transcriptase ("RT"). 429 F.3d at 1071–72. The Federal Circuit reversed the district court's summary judgment of lack of written description, where the patents-in-suit disclosed the DNA and amino acid sequence for RT and there was evidence that members of the RT gene family had species to species commonality, and where the patent disclosed tests to determine whether a modified RT had the desired activity and test results for some examples. *Id*. at 1073. Here, too, the Fiers '755 Patent discloses the DNA and amino acid sequence of IFN-β, requires the IFN-β muteins to be significantly homologous to IFN-β, and discloses tests that can be run to assess whether the muteins have the desired antiviral activity and data demonstrating antiviral features of certain polypeptides within the genus.

* * * *

Without a categorical rule of law, Bayer must seek summary judgment on the facts, showing that the evidence is so lopsided that a jury would have to rule in Bayer's favor. Biogen turns next to that argument.

III. A Jury Could Find That Bayer Has Failed To Prove a Lack of Written Description by Clear and Convincing Evidence

A. The Fiers '755 Patent Contains Adequate Description of IFN-β Muteins

Bayer argues that Dr. Fiers did not possess or contemplate any IFN-β muteins. (Br. at 18.) Specifically, Bayer incorrectly argues that "one—and only one—member of the genus," IFN-β itself, is described. (*Id.*) Then Bayer argues that this supposedly-sole-disclosed species cannot support a genus that is "densely populated" and "includes trillions of trillions of polypeptides." (*Id*. at 19.) Biogen disputes every aspect of that, and has fact and expert evidence from which a jury could reject Bayer's defense.

1. The Fiers '755 Patent Discloses More Than One Species

The jury will be given evidence showing that the Fiers '755 Patent specification discloses the use of several recombinant polypeptides within the scope of Claim 1, not just one. For example, the Fiers '755 Patent discloses examples of three different recombinant DNA molecules that express IFN-β-like recombinant polypeptides that have HuIFN-β-like antiviral activity. *See, e.g.*, Ex. 1 (Fiers '755 Patent), col. 29:64–45:52. The Fiers '755 Patent further discloses that IFN-β polymorphs can be isolated and then recombinantly expressed to produce IFN-β-like polypeptides, which can then be used in a method of treatment. *See, e.g.*, *id*. col. 25:54–26:3. Biogen's expert Dr. Green will testify that, from Dr. Fiers's disclosures, a skilled artisan would know how to use the clones described in the Fiers '755 Patent as probes to find IFN-β polymorphs and then to recombinantly express those polymorphs and assay them for biological activity.

Green Decl. ¶ 124-25.

The Fiers '755 Patent also discloses methods of using IFN-β muteins that differ by one or more amino acids from IFN-β, or that are longer (or shorter) than IFN-β, and yet have the biological or immunological activity of HuIFN-β. *See, e.g.*, Ex. 1 col. 48: 22–27. The patent discloses that the muteins could possibly "increase the stability, increase the solubility, increase the antiviral activity, increase [the] 2,5-A synthetase activity or increase the host specificity range." *See, e.g.*, *id.* col. 48:22–27; *see also id.* col. 15:1–10. The Fiers '755 Patent teaches that these IFN-β muteins can be made "by well-known means." *Id*. col. 48:36–41.

In addition to disclosing complete and partial structures of the IFN-β muteins, the Fiers '755 Patent describes various other blaze marks by which a skilled artisan could find her way to additional IFN-β muteins that can be used to practice the method of Claim 1. The Fiers '755 Patent discloses functional characteristics of the IFN-β muteins: they must have antiviral activity like HuIFN-β. *Id.* Abstract, col. 1:13–28, 6:47–53, 7:8–14; Green Decl. ¶¶ 125-26; Garcia Decl. ¶ 61. The Fiers '755 Patent also discloses the physical and/or chemical properties of the IFN-β muteins: they must be physically and chemically similar to IFN-β, *i.e.*, the amino acid sequence for the IFN-β muteins must be nearly identical chemically and physically to IFN-β, such that the DNA that encodes the IFN-β mutein is capable of hybridizing to DNA inserts comprising essentially IFN-β. Ex.

1 (Fiers '755 Patent), col. 1:19–24, 7:15–36; Green Decl. ¶¶ 112, 124-125; Garcia Decl. ¶¶ 55-68.

Bayer asserts that "it is undisputed that there was no structure-function correlation at all disclosed in the patent," (Br. at 25), but that is absolutely disputed. The Fiers '755 Patent discloses a correlation between function and structure. *See, e.g.*, col. 4:39–46 (noting that IFN-β and IFN-α have a shared "common active core"). Moreover, as Biogen's experts will testify, by June 1980 ordinarily skilled artisans would have known several guideposts for such correlation. For example, the skilled artisan would have known that the functional biological activity of IFN-β and its muteins is tied to various known structural features, including having a common structural core with other interferons, as well as having the disulfide bond necessary for biological activity. Green Decl. ¶¶ 112, 124-125; Garcia Decl. ¶¶ 55-68. Moreover, the skilled artisan would have known various computational means to reasonably predict the correlations between function and structure. Green Decl. ¶¶ 112, 124-125; Garcia Decl. ¶¶ 55-68.

2. The Genus of Usable IFN-β Muteins Is Narrower than Bayer Asserts

Bayer makes much of the assertion that Claim 1 encompasses the use of a "trillions of trillions of polypeptides." (Br. at 19.) The jury will hear conflicting evidence about this, too, and could easily reject Bayer's argument.

For example, Dr. Green and Dr. Garcia opined in their expert reports that

Claim 1 covers the use only of IFN-β variants such as IFN-β polymorphs and conservative mutations. Green Decl. ¶¶ 112, 124-125; Garcia Decl. ¶¶ 55-68. They cite portions of the Fiers '755 Patent that disclose examples of such recombinant polypeptides and teach guideposts so that "one of skill in the art can 'visualize or recognize' the members of the genus." *Ariad*, 598 F.3d at 1350; *Regents of the Univ. of Cal*. v. *Eli Lilly & Co*., 119 F.3d 1559, 1568 (Fed. Cir. 1997). Such guideposts include disclosures regarding IFN-β polymorphs and conservative mutations intended to optimize stability, solubility, and the like.

Bayer acknowledges that Biogen's experts believe the claim scope to be narrow. (Br. at 6–7.) Yet, Bayer essentially argues that it does not matter what a person of skill in the art would understand the claim scope to be. (*Id*. at 7.) Rather, Bayer argues that the Fiers '755 Patent lacks written description because it covers the use of potentially trillions of trillions of diverse muteins that are only limited by function. Bayer cites various cases in support.[6]

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[6] *See* Br. at 15–17, 19 (citing *AbbVie Deutschland GmbH & Co.* v. *Janssen Biotech, Inc.*, 759 F.3d 1285 (Fed. Cir. 2014) (claiming a structurally diverse genus of antibodies to IL-12 when only a subset of antibodies were disclosed); *Novozymes A/S* v. *DuPont Nutrition Biosciences APS*, 723 F.3d 1336 (Fed. Cir. 2013) (claiming variants of BSG α-amylase when only structurally diverse BLA α-amylase variants were disclosed); *Centocor Ortho Biotech, Inc.* v. *Abbott Labs*., 636 F.3d 1341 (Fed. Cir. 2011) (claiming humanized TNF-α antibodies when only structurally diverse chimeric or mouse derived TNF-α antibodies were disclosed); *Ariad,* 598 F.3d at 1351 (claiming the use of a structurally diverse genus of substances that reducing NF-κB activity when only three hypothetical, yet structurally diverse, molecule types were disclosed); *In re Alonso*, 545 F.3d 1015

None of those cases is determinative here. Notably only *Rochester* was a decision on summary judgment. *In re Alonso* was an appeal of the PTO Board's decision during the examination of a patent application. The other cases were based on a fully developed record after trial. And all of Bayer's cases analyze claims directed to structurally disparate groups of molecules related solely by desired function, without any meaningful guideposts as to which molecules would fall within that functional genus. In contrast, Biogen will present evidence that the population of recombinant polypeptides covered by the method of treatment claim is very tightly related to HuIFN-β functionally ***and*** structurally. The DNA that encodes the IFN-β mutein must be nearly identical to HuIFN-β, and thus the amino acid sequence for the IFN-β mutein must be nearly identical. The structure of the folded IFN-β mutein must be nearly identical to HuIFN-β, so that the IFN-β mutein can function like HuIFN-β. *See, e.g.*, Ex. 1 col. 1:19–24; Green Decl. ¶¶ 112, 124-125; Garcia Decl. ¶¶ 55-68. And, unlike in Bayer's cases, the Fiers '755 Patent disclosed specific working examples of recombinant polypeptides that have HuIFN-β-like activity and provided guideposts for additional embodiments within

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(Fed. Cir. 2008) (claiming antibodies to a structurally diverse genus of neurofibrosarcoma cells when only antibodies to specific neurofibrosacroma cells were disclosed); *Rochester* (claiming a genus of structurally diverse COX-2 inhibitors when disclosing no such inhibitor); *Regents of the Univ. of Cal.* v. *Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997) (claiming a genus of hosts transformed with a structurally diverse genus of cDNA that encodes all vertebrate and mammalian insulin when disclosing only rat insulin cDNA).

the claimed genus. *See, e.g.,* Ex. 1 (Fiers '755 Patent), col. 29:64–45:52, 2:32–39, 25:54–26:3, 48:22–27; *see also* Biogen's response to Bayer's Statement of Undisputed Facts at 13–16. The Fiers '755 Patent also teaches a robust assay to determine which of the closely-related IFN-β muteins would have the desired function, antiviral activity. *See, e.g.,* Ex. 1 col. 36:1–34.

3. Uncertainty About Whether a Particular IFN-β Mutein Has Antiviral Properties Prior to Testing Does Not Render the Patent Invalid

According to Bayer, the Federal Circuit "frequently" invalidates biopharmaceutical genus claims as a matter of law "where they define a genus of the claim using functional language rather than structural language." (Br. at 15.) If the genus of Claim 1 is described only functionally, Biogen must prove, according to Bayer, that there is an established structure-function relationship. None of this matters, because Claim 1 is not defined solely by functional language, but instead defines recombinant polypeptides both structurally and functionally. And Bayer vastly over-reads the cases. While it is true that claiming a functional genus is permissible when "there is an established correlation between structure and function," Bayer errs in asserting the converse, namely that without an established structure-function correlation, a functional limitation is per se inadequate. (*See Id*. at 9–10, 25.) None of Bayer's cases supports that proposition.

One of the basic tenets of scientific research is that nothing is 100%

predictable—scientific hypotheses, no matter how robust, must be empirically tested. Despite some level of unpredictability regarding whether certain IFN-β muteins would be active, at the time of Dr. Fiers's invention in June of 1980, a skilled artisan had sufficient guideposts to determine a reasonable relationship between IFN-β structure and its activity. For example, Dr. Green and Dr. Garcia will testify that one of skill in the art would understand which mutations were conservative mutations based on, for example, sequence alignments with other interferons, standard mutagenesis studies, and computational modeling. Green Decl. ¶ 125; Garcia Decl. ¶¶ 61-67. Moreover, the Fiers '755 Patent discloses that it was within the skill of those in the art to make minor variants in the DNA that encodes IFN-β and disclosed a way to assay the resulting protein for antiviral activity. *See, e.g.*, Ex. 1 (Fiers '755 Patent), col. 37:17–45:52.

Thus, there is evidence that a skilled artisan would be able to envisage the contours of the polypeptides that can be used for treatment pursuant to Claim 1 of the Fiers '755 Patent based on the patent specification and general knowledge in the art at the time. Bayer has not provided any undisputed facts that the claims are not adequately described by clear and convincing evidence.

4. At Most, Bayer's Motion Demonstrates That There Are Disputed Issues of Fact

Contrary to Bayer's assertions, the undisputed facts do not establish that Claim 1 of the Fiers '755 Patent lacks written description. Bayer's attempt to hide

the disputed issues of material fact—*e.g.*, the size of the genus, the sufficiency of the guideposts in the Fiers '755 Patent—should be rejected. *Enzo,* 323 F.3d 956 is on point. There, the Federal Circuit reviewed the district court's summary judgment decision invalidating genus claims for failure to meet the written description requirement. *Id*. The claims were directed to a genus of nucleic acid probes that selectively hybridize to the genetic material of the bacteria that causes gonorrhea. *Id*. at 961. Like here, one of the claims included "mutated discrete nucleotide sequences of any of the [deposited sequences] that are within said hybridization ratio and subsequences thereof." *Id*. at 962. Although there was testimony that "'astronomical' numbers of mutated variations of the deposited sequences also fall within the scope of those claims," it was recognized that "such broad claim scope is necessary to adequately protect [patentee's] invention from copyists who could otherwise make a minor change to the sequence and thereby avoid infringement while still exploiting the benefits of [patentee's] invention." *Id*. at 966. The Federal Circuit thus held that "it may well be that various subsequences, mutations, and mixtures of those sequences are also described to one of skill in the art." *Id*. As a result, the Federal Circuit reversed the district court's grant of summary judgment: "We regard that question as an issue of fact that is best resolved on remand." *Id*.

Bayer argues that "the Federal Circuit's decision in *Boston Scientific*

compels judgment for Bayer." (Br. at 24.) It does not. There, the specification itself conceded that the relationship between the structure of the compound rapamycin and its mechanism of action were unknown. *Boston Scientific*, 647 F.3d at 1366. Thus, the court concluded "when the four corners of the specification directly contradict information that the patentee alleges is 'well-known' to a person of skill at the effective filing date, no reasonable jury could conclude that the patentee possessed the invention." *Id*. That is not the case here. Here, the Fiers '755 Patent specifically states that a person of skill would understand IFN-β's necessary structural core: "Both IFN-β and IFN-α appear to trigger similar enzymatic pathways and both may share a common active core because they both recognize a chromosome 21-coded cell receptor." Ex. 1 (Fiers '755 Patent), col. 4:39–46 (internal citations omitted). Biogen's experts, Dr. Green and Dr. Garcia agree. This alone is sufficient to defeat Bayer's motion for summary judgment.

CONCLUSION

For the reasons set forth above, Biogen respectfully requests that the Court deny Bayer's Third Motion for Summary Judgment for Invalidity based on written description.

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